REMARKS

The Office action dated July 16, 2003 is acknowledged. Claims 1-15 are pending in the instant application and claims 16-28 have been added. According to the Office action, claims 1-15 have been rejected. Reconsideration is respectfully requested in light of the following remarks.

Rejection of Claims 1-15 under 35 U.S.C. 103 (a)

Claims 1-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,503,844 (Kwiatek et al.). It is respectfully submitted that these claims are patentably distinct from the prior art reference.

The Examiner states that Kwiatek et al. '844 teaches the use of a transdermal therapeutic patch for the controlled release of lovastatin to the skin or mucuous membranes wherein the transdermal patch contains active substance(s), a backing layer, active agent permeable adhesive layer(s), rate-controlling polymers and a means whereby the transdermal patch has a high degree of uniformity and consistency for critical transdermal properties such as release rate, and refers to col. 1, line 45 – col. 2, line 25; col. 11, line 47 – col. 12, line 55; col. 16, lines 30 – 40; col. 17, lines 5 – 12; and col. 24, lines 20 – 26. The Examiner further states that Kwiatek et al. '844 teaches that each active agent permeable adhesive layer is a pressure-sensitive adhesive layer and that any of the well-known, dermatologically acceptable, pressure-sensitive adhesives that permit drug migration therethrough can be used.

The Examiner also states that Kwiatek et al. '844 teaches up to a 24-hour release profile of nicotine flux through the skin and also teaches the theory of how to control the rate of release. Additionally, the Examiner states that the reference teaches that the transdermal

patch is produced efficiently with little variation in release rate and that the patch offers uniformity and consistency for release rate properties (col. 1, lines 45 – 60). The Examiner concludes that there is no significant distinction observed between the instant invention and that of Kwiatek et al. '844 since the reference teaches a transdermal therapeutic patch containing an active ingredient which influences blood lipid levels, lovastatin, wherein the patch comprises a backing layer, active agent permeable adhesive layer(s) and rate-controlling polymers wherein the active is contained within the pressure-sensitive adhesive layers. Furthermore, according to the Examiner, Kwiatek et al. '844 teaches a release profile of up to 24-hours and the theory of how to control rates of release and consistency of release rates. As such, the Examiner considers the present invention obvious and unpatentable in light of Kwiatek et al. '844, as discussed in greater detail below.

Applicant respectfully points out that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references when combined must teach or suggest all of the claim limitations.

Applicant respectfully disagrees with the Examiner's conclusion set forth above. Applicant wishes to emphasize that the active substance of the present invention is contained in a matrix layer, this feature not being taught or disclosed by Kwiatek et al. '844. Moreover, the applicant submits that this is the most distinguishing feature between the present invention and the cited reference and that it would not be obvious to one skilled in the art to adopt this feature in the invention disclosed by Kwiatek et al. '844.

Applicant respectfully explains that a transdermal therapeutic patch for administering a drug for an extended period of time comprises a backing layer which is substantially impermeable to the drug and which forms the top or outer surface of the patch, a reservoir layer for securing the active drug, and a structure exhibiting some rate controlling property for the controlled release of the active drug. As the Examiner is well aware, the reservoir layer may be a membrane bag type reservoir wherein the drug is enclosed therein by a membrane which controls the release of the drug. Such a patch is provided with an additional layer of a pressure-sensitive adhesive for adhering this bag-type system to the patient's skin. As the Examiner is also well aware, an alternative type of transdermal therapeutic system is a patch comprising a matrix-type reservoir wherein the drug is dispersed in a pressure-sensitive adhesive polymer and released from the matrix by diffusion. Thus, the matrix layer of the present invention is able to fulfill all three functions of being a reservoir for the active compound, being a means of control for the controlled release of the drug and being the means for adhering the system to the patient's skin.

Applicant also respectfully submits that the aforementioned descriptions and terms are well known in the art and are commonly employed in the field of manufacturing transdermal therapeutic patches. Moreover, the applicant submits that the term "matrix" would clearly be understood by one skilled in the art as a layer comprising the active compound dispersed in a self-adhesive polymer, the layer being attached to the patient's skin and being the means for controlling the release of the active compound to be administered. Furthermore, the applicant submits that one skilled in the art would understand, when reviewing the present specification and based on his or her knowledge in the art, that the

matrix layer serves as a reservoir for the active substance, in the case of the present invention.

Referring now to the prior art reference, applicant submits that in contrast to a matrix-type reservoir system according to the present invention, the transdermal drug delivery patch of Kwiatek et al. '844 comprises a foam layer that serves as a reservoir for the active substance. Moreover, the patch of Kwiatek et al. '844 must comprise at least one additional adhesive layer as a means for attaching the patch to the patient's skin since the foam reservoir is not self-adhesive. The presence of an additional rate-controlling layer for controlling the release of the drug is desired and strongly emphasized throughout Kwiatek et al. '844. For example, nearly each of the figures depicts foam patches comprising an additional rate-controlling layer.

Kwiatek et al. '844 also discloses that the additional adhesive layer may contain some of the active agent to provide an immediate absorption of the active agent. However, Kwiatek et al. '844 neither teaches or even suggests that the adhesive layer can be a reservoir for the active agent. Even in regards to the presence of active agent within the adhesive layer, the presence of a rate-controlling layer is emphasized (col. 12, lines 37 – 52). Applicant submits that this would strongly indicate to one skilled in the art that it is not the adhesive layer that controls the release of active agent from a patch according to Kwiatek et al. '844. The reference does not even suggest any motivation to one skilled in the art to refrain from employing the foam layer as a reservoir for the active agent and to utilize the adhesive layer instead.

Applicant would like to further submit that the foam laminate transdermal patch according to Kwiatek et al. '844 is compared to a coextruded monolithic nicotine patch, and refers to Example 4 in order to illustrate the advantages of the foam laminate transdermal patch over monolithic patches. Applicant submits that it is known in the art that a monolithic patch is synonymous with a matrix type patch and it appears that the disclosure of Kwiatek et al. '844 distinguishes between the foam laminate transdermal patch and the matrix-taper reservoir patches, such as those of the present invention. Applicant further submits that it can be inferred from the examples within the instant specification that the patches of the present invention are monolithic/matrix type systems.

In the Office action, the Examiner reiterates that Kwiatek et al. '844 discloses a patch providing uniform and constant release of the active substance. However, applicant also respectfully disagrees with the Examiner's conclusion for at least the reasons set forth above. Moreover, applicant would like to refer to Tables I and III of Kwiatek et al. '844. These tables provide data for the release kinetics of nicotine over a 24-hour period and clearly illustrate that a transdermal patch according to Kwiatek et al. '844 is not capable of providing an essentially constant release of active substance over a 72-hour period. In order to emphasize this point, the applicant provides the following explanatory tables which present the data of Tables I and III in an alternative manner, and which were also provided in the response to the previous final Office action.

Table I

Nicotine In-Vitro FLUX Through Skin (mg/10 cm^2 X hr)

	2 hr. period	4 hr. period	9.5 hr. period	24 hr. period
Example	0.545	0.6525	0.583	0.365

Table III

Nicotine In-Vitro FLEX Through Skin (mg/10 cm^2 X hr)

	2 hr. period	4 hr. period	8 hr. period	24 hr. period
Example 2	0.31	0.315	0.2675	0.195
Example 3	0.435	0.445	0.406	0.321
Example 4	0.54	0.5825	0.406	0.48

It is clear from the explanatory tables that Tables I and III demonstrate that the average hourly release during a 24-hour period is significantly lower than the average hourly release during a 2-hour or 4-hour period. Given that the hourly release at the beginning of a 24-hour period is not as high as the hourly release during the 2-hour or 4-hour period, it appears that the release rate at the end of the 24-hour period is even lower than the average release during the entire period. Thus, a patch according to Kwiatek et al. '844 is not able to provide an essentially constant release rate over a 24-hour period. Applicant submits that it would naturally follow that if the patch of Kwiatek et al. '844 cannot provide a constant

release rate over a 24-hour period, then it would not be able to provide a constant release rate over a 72-hour period either.

Applicant also points out that although the data was acquired with nicotine as the active substance, there is no indication in the reference that this release kinetic is active substance dependent. To the contrary, applicant submits that there is no indication in the reference that the release kinetics for other active substances such as HMG-CoA reductase inhibitors, or other substances having an influence on blood lipid levels, would be different.

Applicant would additionally like to point out that with reference to Table I, the hourly release of 0.365 mg/10 cm^2 (for the 24-hour period) constitutes only 56% of the hourly release at the 4-hour period (0.6525 mg/10 cm^2 (set at 100%)). A reduction of flux of about one-half of the maximally observable flux (at the 4^{th} hour) within the 24-hour period cannot be considered uniform and constant at all. Applicant further points out that Kwiatek et al. '844 does not address this point and does not provide any suggestion towards maintaining a constant flux over a period of over 24 hours, let alone 72 hours.

In summary, the applicant does not believe that Kwiatek et al. '844 teaches or suggests the matrix type reservoir system for transdermal administration of active agents wherein the active agent is dispersed in a self-adhesive polymer matrix which serves as a reservoir for the active-agent as well as a means for adhering the patch to the patient's skin, nor would the same have been obvious to one skilled in the art at the time the present invention was made. It is also apparent that the reference provides no suggestion or motivation to modify the invention of Kwiatek et al. '844 to make up for the aforementioned deficiencies, nor would there be a reasonable expectation of success if one skilled in the art

were to attempt to modify the reference. Furthermore, the term "polymer matrix layer," as provided in amended claim 1 and new claim 16, is a clear and unambiguous feature to one skilled in the art and precisely characterizes the patch of the present invention in contrast to the foam laminate transdermal patch according to Kwiatek et al. '844.

In order to emphasize the inventiveness of the transdermal therapeutic patch of the present invention when compared to that of Kwiatek et al. '844, the applicant has included the term "said preparation serves as active substance reservoir" in independent claim 1, upon which claims 2-13 depend, support for which may be found in the specification at page 5, line 7. It is the applicant's belief that claim 1, as amended, now clearly illustrates this feature of inventiveness of the present invention and sufficiently differentiates the present invention from that of the cited prior art.

Applicant has also submitted new claim 16 as indicated above and its dependent claims 17-28, which distinctly set forth the present invention.

Conclusion

For the foregoing reasons, it is respectfully submitted the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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